REMARKS

Claims 1-6 currently appear in this application. The Office Action of October 31, 2007, has been carefully studied. These claims define novel and unobvious subject matter under Sections 102 and 103 of 35 U.S.C., and therefore should be allowed. Applicant respectfully requests favorable reconsideration, entry of the present amendment, and formal allowance of the claims.

Rejections under 35 U.S.C. 112

Claim 6 is rejected under 35 U.S.C. 112, second paragraph, for being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention.

This rejection is respectfully traversed. Claim 6 has been amended to recite "at least one" rather than "one or more" steps.

Art Rejections

Claims 1 and 3 are rejected under 35 U.S.C. 102(b) as anticipated or, in the alternative, under 35 U.S.C. 103(a) as being obvious over Quirion et al., *Tetrahedron Letters*, 2001, 42, 5879-5882.

Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Quirion in view of Wong et al., *Bioorganic & Medicinal Chemistry* Letters, 1998, **8**, 2333-2338.

Claims 4-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lerner et al., *J. Org. Chem.* 1979, **44(19)**, 3368-3373 in combination with Furstner, *Synthesis*, 1989, 571-590.

These rejections are respectfully traversed.

In the pending official letter the Examiner is of the opinion that Marcotte et al. teaches a C-glycosides (structure 1) having a CF_2 group and an alkyl chain that is functionalized with an amine group and an acid function.

In fact this publication only shows that at the moment of the publication Marcotte and Al. were still studying a solution for using a difluoromethylene group in place of the anomeric oxygen bond and preparing a new glycoconjugate derivative usable for medicinal purpose and that such a solution were not discovered yet.

This fact is clearly precised in this publication which states that:

"However, a general synthesis of gem-difuoromethylene C-glycosides applicable to the most often encountered carbohydrates is still to discover."

"We reasoned that gem-difuoroesther would be valuable starting materials for the preparation of the corresponding amine acid 1..." (this sentence is only hypothetic and does not constitute a result).

"In a first attempt... but all our attempts failed whatever the conditions."

"With aldehyde 6 we then studied the attack of the ethyl bromodifluoroacetate in the presence of activated Zn dust...but this method failed."

"We also tried the Reformatsky-type reaction using SmI_2...but there was no improvement in the stereo selectivity."

"However these compounds gave us an access to both α and ß difluorometylene C-glycosides... We envisaged two different procedures for the cyclisation step.

The first one involved the formation of an expoxide... We were unable to improve the diastereoselectivity whatever the conditions of epoxide formation."

In fact the sole teaching of Marcotte is that :

"an access to the α and β-gem-difluorometylene C-glycosides has been developed. A stereoselective ring formation via an intramolecular oxymercuration was the key step."

However the transformation of HgBr into OH used in Marcotte is not applicable to medicinal compounds (presence of Hg) and never leads to the claimed stereoisomer.

This fact is confirmed by Marcotte which states that:

"we are also studying new method for cyclization to avoid the use of mercury salts and the application of this strategy to other biologically interesting carbohydrates."

It can be concluded from Marcotte that

1/ The applicant's invention was not discovered at the date of the Marcotte's publication.

2/ The research made by Marcotte raised numerous problems without solution.

3/The obtention of a solution usable for medicinal purpose (as the applicant's claimed solution) is not obvious for one skilled on the art.

For the above mentioned reason Marcotte cannot render evident the applicant's invention but only reveals a starting point of research which in spite of numerous prejudged has been successfully conduced more than one year later to obtain the applicant's claimed solution.

Claim 1 was amended with R2=OH or OR with R is a protecting group.

There is no common structure between the claimed compounds and all the derivatives described in Marcotte and Marcotte's process does not allow access to a structure similar to the applicant's claimed structure due to the fact that the claimed solution does not consist in fully replacing the anomeric oxygen in classical sugar (it is still in the claimed structure) by a CF2, as in Marcotte, but to develop a new sugar mimic in which the sugar still bears an oxygen at the anomeric position.

Provided that now, on this position, there are two substitutions: oxygen as in natural sugar and a CF2-R1.

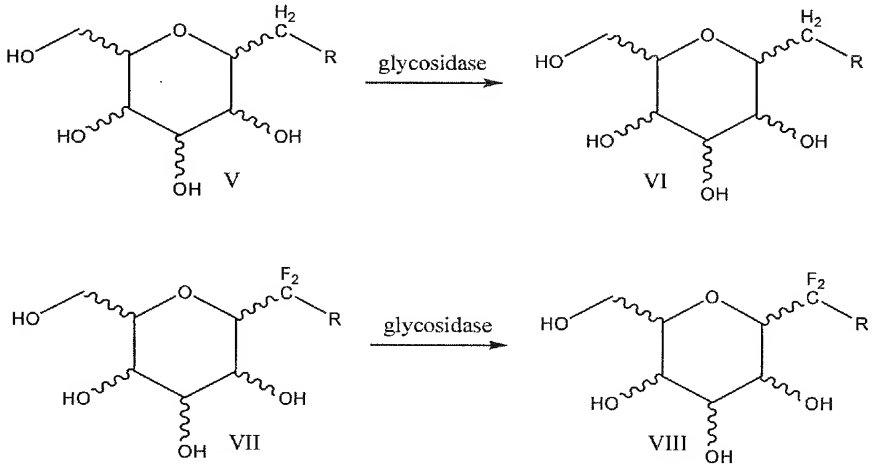
This is very important: This allows the sugar to act as natural sugar in solution and to undergo opening and closing reactions thanks to this oxygen, and to possess also a side chain, which cannot be cleaved by enzymes (glycosidase) or acido-basic hydrolysis with this CF2 giving an electronegativity close to oxygen (which is not the case with CH2 sugar described in Lerner and Wong), and furthermore Fluor atoms allow new types of interaction with protein receptors.

A closer look at natural sugar, as in formula I, shows that these compounds, by action of glycosidase, undergo cleavage of the side chain R, and lead to the sugar being separated from the aglycone part R, and which is in solution under three different forms such as: 6 membered ring

(pyranose) formula II with the OH in α or in β, the linear formula III, and the 5 membered-ring (furanose) formula IV with the OH in α or in β. Depending on the sugar, two major formulas are found formula II and formula IV.

This is the classical behaviour of natural sugar in solution if there is protecting group on the sugar. It could be "prima facie" deduced that it is the same behaviour. However it appears that it is the same behaviour except that formula IV does not exist because the oxygen which allows such cyclisation is protected.

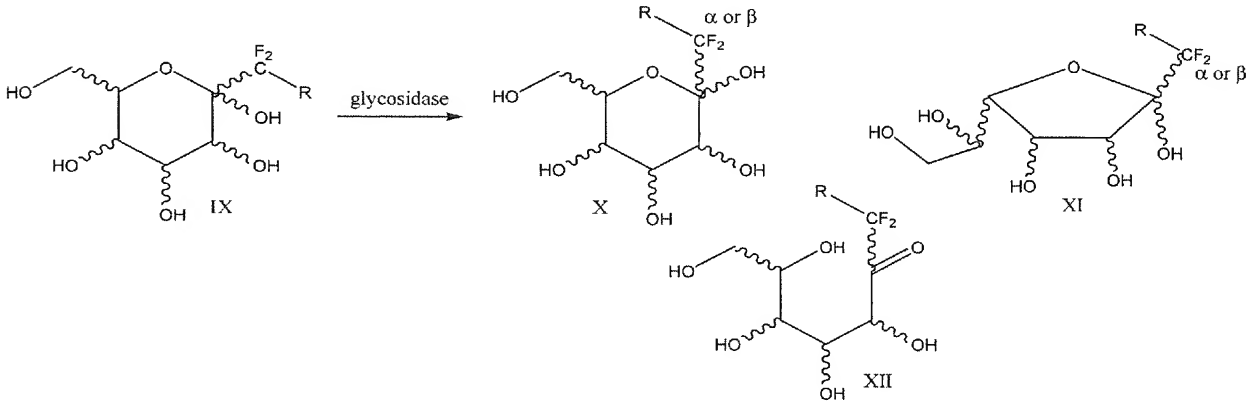
Concerning CH2 (Wong) or CF2 sugar (Marcotte) already described:



First, nothing happened in the CH2 or CF2 series, because both of them are resistant against degradation (enzymatic or acido-basic hydrolysis), and nothing more: they

don't behave as natural sugar in solution because of the OH missing in the anomeric position.

In the applicant's claimed compound, which bears CF2 and OH at the anomeric position, this is quite different, because the claimed compound benefits at the same time of the stability due to the CF2, provided that the R is not removed, but undergoing the same behaviour as natural sugar in solution. This acts as real sugar which is really different from what is observed in the case of Marcotte, Lerner or Wong. In this case also and, depending on the sugar, two major forms X and XI are found.



If the oxygen at the anomeric position bears a substituent such as R, then it will be cleaved in the presence of glycosidase, and it will lead then to the OH, and undergo the same behaviour as natural sugar in solution.

It is emphasised on the fact that CH2 is really different from CF2 and in that it is not only a matter of stability:

Introduction of fluorinated atoms in medicinal chemistry leads to the discovery of numerous drugs. It is present in 20 to 30% of drugs on the market. Modifications obtained by the introduction of fluorinated atoms in organic compounds have an important role in their behaviour in biological media:

- Improvement of metabolic stability
- Modifications of physicochemical properties: such as acidity and basicity of neighbouring functions that have a strong effect on pharmacokinetic properties.
- Direct and indirect impact on interactions between fluorine and proteins, which reinforce affinity for receptor.

Several compounds are known in which the fluorinated atom brings advantages in term of efficiency, selectivity, biological activity, and less disfavorable effects than in parent compounds without fluorine.

This underlines CH2 is really different from CF2 in these effects, and that it is not only a matter of stability.

Comparing Furstner, Lerner and Wong to the applicant's solution it cannot be concluded that CH2 is identical to CF2, which is inappropriate for one skilled of the art or that a fluorine is identical to a hydrogen.

H and F have in common their small size, but everything else is extremely different: electronegativity (F is the most electonegative atom of the periodic table), polarisability (F is the less polarisable atom). The extreme properties of fluorine lead one skilled of the art to understand that such atoms will react in a totally different way, than other atoms.

It is also well known from one skilled of the art who is a specialist in fluorine chemistry, that a carbon bearing two fluorine atoms is a bad nucleophile, provided that to react a strong electrophile is necessary.

Lets try now to apply this to the Furstner publication, which deals with BrCH2CO2Et:

Reformatsky reaction is a well known and classical reaction with BrCH2CO2Et, and has also been adapted to BrCF2CO2Et. However at the time the patent application was filed this reaction only applied in the case of BrCF2CO2Et to very good electrophiles such as ketones or aldehyde. It was evident to one skilled in the art that a lactone (and especially a lactone of sugar) was not suitable for such a

reaction as not a being good electrophile. To make the reaction work, the experimental part reveals that the BrCF2CO2Et should be added to the refluxing solvent containing Zinc, at the same time or after the lactone. It is impossible to generate is to make the BrCF2CO2Et react on to the Zinc, and to add the lactone after, which is however classical in Reformatsky with BrCH2CO2Et. The reactivity is totally different.

In addition, this reaction has never been performed on lactone before the applicant's patent application, and furthermore, it doesn't work on every kind of lactone.

It is a new process because CH2 and CF2 are really different structurally as well in term of reactivity. The use of BrCF2CO2Et has never been performed on lactone and especially on sugar lactone before the filing date of the applicant's patent application. This patent application leads to a great improvement.

Furthermore, to achieve this reaction numerous trials have been perfomed by changing concentration, heating, the order of addition of reagents. Reactivity of ketones and aldehydes are extremely different from lactone, and this reaction does not succeed with all sort of lactones: for example it works with a 6-membered ring lactone, but not with a 5-membered ring lactone in the case of sugar.

In Lerner, as seen previously, Reformatsky reaction is known with BrCH2CO2Et on lactone sugar, but this is different than BrCF2CO2Et.

In the applicant's case, the Reformatsky using BrCF2CO2Et has never been performed on lactone and sugar lactone. The Lerner publication deals with 5 membered ring sugar lactone, and the applicant is sorry to say that he was unable to succeed the Reformatsky reaction with BrCF2CO2Et on this type of lactone. This confirms that it is different and not evident for one skilled of the art.

Then comes the Wong publication, with C-glycopeptides, meaning CH2-glycopetides, which are really different from what the applicant did. First, it is not the only one to work on C-glycoside, there are patents, publications dealing with this subject. But it has to be kept in mind as previously described that the applicant's claimed compound has an additional O on the anomeric position. This makes a first fundamental difference but not only.

Thus the new applicant's sugar mimic, bearing an oxygen on the anomeric position and a CF2 with a side chain is the applicant's innovation. This has never been done before in term of compounds and in time of processes. This result was difficult to achieve and nobody could predict the results.

In addition the applicant's claimed solution is directed to CF2-glycosides and glucopeptides.

In view of the foregoing, early and favourable reconsideration of this office action together with the allowance of the previously amended claims 1 to 7 is respectfully solicited.

Respectfully submitted,

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